WHAT IS CLAIMED IS:

1. An antigen-specific tolerogenic compound for the induction of antigen-specific immune tolerance in a subject, the compound comprising:

an antigen to which tolerance is desired;

wherein the antigen to which tolerance is desired, when presented alone to the subject is capable of inducing an unwanted immune response in the subject;

a polymeric linker comprising:

a copolymer comprising a first acrylyl unit and a second acrylyl unit, the first acrylyl unit comprising a first C-amido or C-carboxy functionality and the second acrylyl unit comprising a second C-amido or C-carboxy functionality;

wherein the second C-amido or C-carboxy functionality is conjugated to an aliphatic group, an alcohol, or an aliphatic alcohol;

wherein the polymeric linker is bonded to the antigen to which tolerance is desired via a disulfide bond or a disulfanyl ethyl ester;

wherein the polymeric linker comprises a terminal end unit lacking each of a dithioester and a dithiobenzoate (DTB) and wherein the terminal end unit confers improved stability to the compound when in solution; and

a liver-targeting moiety;

wherein the liver targeting moiety is connected to the first acrylyl unit through the first C-amido or C-carboxy functionality and a polyether.

2. An antigen-specific tolerogenic compound for the induction of antigen-specific immune tolerance in a subject, the compound comprising:

an antigen to which tolerance is desired;

wherein the antigen to which tolerance is desired, when presented alone to the subject is capable of inducing an unwanted immune response in the subject, wherein the antigen to which tolerance is desired is associated with Celiac Disease;

a polymeric linker comprising:

a copolymer comprising a first acrylyl unit and a second acrylyl unit, the first acrylyl unit comprising a first C-amido or C-carboxy functionality and the second acrylyl unit comprising a second C-amido or C-carboxy functionality;

wherein the second C-amido or C-carboxy functionality is conjugated to an aliphatic group, an alcohol, or an aliphatic alcohol;

wherein the polymeric linker is bonded to the antigen to which tolerance is desired via a disulfide bond or a disulfanyl ethyl ester;

wherein the polymeric linker comprises a terminal end unit lacking each of a dithioester and a dithiobenzoate (DTB) and wherein the terminal end unit confers improved stability to the compound when in solution; and

a liver-targeting moiety,

wherein the liver-targeting moiety is a galactosylating moiety or a glucosylating moiety, and

wherein the liver targeting moiety is connected to the first acrylyl unit through the first C-amido or C-carboxy functionality and a polyether.

3. The compound of Claim 2, wherein the antigen to which tolerance is desired comprises one or more of SEQ ID NO. 55, SEQ ID NO. 54, SEQ ID NO. 56, or SEQ ID NO. 57.

4. The compound of Claim 2, wherein the antigen to which tolerance is desired comprises one SEQ ID NO. 55 and wherein the liver targeting moiety comprises N-acetylgalactosamine.

5. An antigen-specific tolerogenic compound for the induction of antigen-specific immune tolerance in a subject, the compound comprising:

an antigen to which tolerance is desired;

wherein the antigen to which tolerance is desired, when presented alone to the subject is capable of inducing an unwanted immune response in the subject, wherein the antigen to which tolerance is desired is associated with Mutliple Sclerosis;

a polymeric linker comprising:

a copolymer comprising a first acrylyl unit and a second acrylyl unit, the first acrylyl unit comprising a first C-amido or C-carboxy functionality and the second acrylyl unit comprising a second C-amido or C-carboxy functionality;

wherein the second C-amido or C-carboxy functionality is conjugated to an aliphatic group, an alcohol, or an aliphatic alcohol;

wherein the polymeric linker is bonded to the antigen to which tolerance is desired via a disulfide bond or a disulfanyl ethyl ester;

wherein the polymeric linker comprises a terminal end unit lacking each of a dithioester and a dithiobenzoate (DTB) and wherein the terminal end unit confers improved stability to the compound when in solution; and

a liver-targeting moiety,

wherein the liver-targeting moiety is a galactosylating moiety or a glucosylating moiety, and

wherein the liver targeting moiety is connected to the first acrylyl unit through the first C-amido or C-carboxy functionality and a polyether.

6. The compound of Claim 5, wherein the antigen to which tolerance is desired comprises one or more of SEQ ID NO. 27, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 43, SEQ ID NO. 44, SEQ ID NO. 45, or SEQ ID NO. 46.

7. The compound of Claim 6, wherein the liver targeting moiety comprises N-acetylgalactosamine.

8. An antigen-specific tolerogenic compound for the induction of antigen-specific immune tolerance in a subject, the compound comprising:

an antigen to which tolerance is desired;

wherein the antigen to which tolerance is desired, when presented alone to the subject is capable of inducing an unwanted immune response in the subject, wherein the antigen to which tolerance is desired is associated with food allergy or autoimmune disease;

a polymeric linker comprising:

a copolymer comprising a first acrylyl unit and a second acrylyl unit, the first acrylyl unit comprising a first C-amido or C-carboxy functionality and the second acrylyl unit comprising a second C-amido or C-carboxy functionality;

wherein the second C-amido or C-carboxy functionality is conjugated to an aliphatic group, an alcohol, or an aliphatic alcohol;

wherein the polymeric linker is bonded to the antigen to which tolerance is desired via a disulfide bond or a disulfanyl ethyl ester;

wherein the polymeric linker comprises a terminal end unit lacking each of a dithioester and a dithiobenzoate (DTB) and wherein the terminal end unit confers improved stability to the compound when in solution; and

a liver-targeting moiety,

wherein the liver-targeting moiety is a galactosylating moiety or a glucosylating moiety;

wherein the liver targeting moiety is connected to the first acrylyl unit through the first C-amido or C-carboxy functionality and a polyether.

9. The compound of Claim 8, wherein the antigen to which tolerance is desired is associated with Celiac disease.

10. The compound of Claim 8, wherein the food antigen is selected from the group consisting of high molecular weight glutenin, low molecular weight glutenin, alpha-, gamma- and omega-gliadin, hordein, secalin, avenin, a portion of any of said antigens, and a mimetic of any of said antigens.

11. The compound of Claim 8, wherein the antigen to which tolerance is desired is associated with food allergy, and wherein the food antigen is selected from the group consisting of conarachin (Ara h 1), allergen II (Ara h 2), arachis agglutinin, conglutin (Ara h 6), 31 kda major allergen/disease resistance protein homolog (Mal d 2), lipid transfer protein precursor (Mal d 3), major allergen Mal d 1.03D (Mal d 1), a-lactalbumin (ALA), lactotransferrin, actinidin (Act c 1, Act d 1), phytocystatin, thaumatin-like protein (Act d 2), kiwellin (Act d 5), ovomucoid, ovalbumin, ovotransferrin, and lysozyme, livetin, apovitillin, vosvetin, 2S albumin (Sin a 1), 1 lS globulin (Sin a 2), lipid transfer protein (Sin a 3), profilin (Sin a 4), profilin (Api g 4), high molecular weight glycoprotein (Api g 5), Pen a 1 allergen (Pen a 1), allergen Pen m 2 (Pen m 2), tropomyosin fast isoform, high molecular weight glutenin, low molecular weight glutenin, alpha-, gamma- and omega-gliadin, hordein, secalin, avenin, major strawberry allergy Fra a 1-E (Fra a 1), profilin (Mus xp 1), and a tolerogenic portion of any of said antigens.

12. The compound Claim 8, where the antigen is associated with an autoimmune disease.

13. The compound of Claim 12, wherein the autoimmune disease is selected from the group consisting of multiple sclerosis, Type I diabetes, rheumatoid arthritis, vitiligo, uveitis, pemphis vulgaris, neuromyelitis optica, Goodpasture's Disease, Parkinson's disease, myasthenia gravis, celiac disease, and anti-neutrophil cytoplasmic antibody-associated vasculitis.

14. The compound of Claim 12, where the antigen comprises a self antigen.

15. The compound of Claim 14, wherein the self antigen is is associated with Multiple Sclerosis.

16. The compound of Claim 14, wherein the self antigen is selected from myelin oligodendrocyte glycoprotein, myelin basic protein, proteolipid protein, and a tolerogenic portion of any of said antigens.

17. The compound of Claim 14, wherein the self antigen comprises a tolerogenic portion of myelin oligodendrocyte glycoprotein.

18. The compound of Claim 14, wherein the self antigen is is associated with Type I Diabetes.

19. The compound of Claim 14, wherein the self antigen is selected from insulin, proinsulin, preproinsulin, glutamic acid decarboxylase-65 (GAD-65), GAD-67, insulinomaassociated protein 2 (IA-2), and insulinoma-associated protein 213 (IA-213), ICA69, ICA12 (SOX-13), carboxypeptidase H, Imogen 38, GLIMA 38, chromogranin- A, HSP-60, caboxypeptidase E, peripherin, glucose transporter 2, hepatocarcinoma-intestinepancreas/pancreatic associated protein, S100β, glial fibrillary acidic protein, regenerating gene II, pancreatic duodenal homeobox 1, dystrophia myotonica kinase, islet-specific glucose-6- phosphatase catalytic subunit-related protein, SST G-protein coupled receptors 1-5, myeloperoxidase (MPO), proteinase-3/myeloblastin (PR3), and a tolerogenic portion of any of said antigens.

20. The compound of Claim 14, wherein the self antigen is is associated with pemphis vulgaris.

21. The compound of Claim 20, wherein the self antigen comprises one or more of a tolerogenic portion desmoglein-3, a tolerogenic portion of desmoglein-1, a tolerogenic portion desmoglein-4, desmoglein-3, desmoglein-1, or desmoglein-4.

22. The compound of Claim 14, wherein the self antigen is is associated with myasthenia gravis.

23. The compound of Claim 22, wherien the self antigen comprises one or more of a tolerogenic portion of an acetylcholine receptor, a tolerogenic portion of muscle-specific kinase (MuSK), a tolerogenic portion of lipoprotein receptor-related protein (LRP4), an acetylcholine receptor, MuSK, or LRP4.

~~2.~~24. ~~The~~ A compound according to any one of claims 1 to 23, wherein the compound has improved stability relative to a compound that includes a dithioester moiety that is a remnant of a chain transfer agent (CTA).

~~3. The compound of claim 1, wherein the terminal end unit is isobutyronitrile.~~

~~4.~~25. ~~The~~ A compound according to any one of claims 1 to 23, wherein the disulfide bond or the disulfanyl ethyl ester are each configured to be cleaved upon administration of the compound to the subject and to release the antigen to which tolerance is desired from the polymeric linker.

~~5.~~26. ~~The~~ A compound according to any one of claims 1 to 23, wherein the terminal end unit lacks one or more of a trithiocarbonate and a xanthate.

~~6.~~27. The compound of claim ~~1~~26, wherein, when in a solution of 10 mM sodium acetate and 274 mM sorbitol at a compound concentration of 1 mg/mL, at a temperature of 23 ºC to 27 ºC, the compound degrades less than 5.0% over a period of 28 days.

~~7.~~28. ~~The~~ A compound according to any one of claims 1 to 23, wherein the terminal end unit comprises a carbon atom that is bonded to a carbon of the polymer linker, thereby providing a carbon-carbon bond between the polymeric linker and the terminal end unit.

~~8. The compound of claim 1, wherein the terminal end unit is provided by performing a reaction between an azo compound and a precursor to the polymeric linker, the precursor comprising a dithioester, a dithiobenzoate, a trithiocarbonate, or a xanthate.~~

~~9. The compound of claim 8, wherein the azo compound is azobisisobutyronitrile (AIBN).~~

~~10. The compound of any one of claims 1 to 9, wherein terminal end unit is isobutyronitrile.~~

~~11.~~29. ~~The~~ A compound according to ~~of~~ any one of claims 1 to ~~9~~23, wherein the terminal end unit lacks one or more of a S atom or an aryl group.

~~12. The compound of any one of claims 1 to 9, wherein the terminal end unit is provided on the compound through a reaction between an azo compound and a precursor to the compound.~~

~~13. The compound of claim 12, wherein the azo compound is an azobisalkylnitrile.~~

~~14. The compound of claim 13, wherein the azo compound is azobisisobutyronitrile (AIBN).~~

~~15. The compound of claim 12, wherein the precursor to the compound comprises a dithioester.~~

~~16.~~30. ~~The~~ A compound ~~of~~ according to any one of claims 1 to ~~9~~23, wherein the first acrylyl unit comprises a first ethylacetamido functionality and the second acrylyl unit comprising a second ethylacetamido functionality.

~~17.~~31. The compound of claim ~~16~~30, wherein the liver-targeting moiety is bonded to the polymeric linker through the first ethylacetamido functionality and wherein the liver-targeting moiety is connected to the first acrylyl unit directly or through a connecting group comprising an aliphatic group, a polyether, or a polyamino group.

~~18.~~32. The compound of claim ~~17~~31, wherein the second ethylacetamido functionality is connected to an aliphatic group, an alcohol, or an aliphatic alcohol and wherein the acts as a spacer.

~~19.~~33. A composition comprising a compound according to any one of claims 1 to ~~18~~23.

~~20.~~34. The composition of claim ~~19~~33, wherein the composition comprises a pharmaceutically acceptable carrier.

~~21.~~35. The ~~U~~use of a compound according to any one of claims 1 to 23~~18~~ in the manufacture of a medicament for ~~use in inducing tolerance to the antigen~~the treatment of an unwanted immune response.

~~22. A method of inducing tolerance to an antigen to which a subject is capable of developing an unwanted immune response, comprising administering a compound according to any one of claims 1 to 18 to the subject.~~

~~23. The method of claim 22, wherein the compound is administered prior to the subject being exposed to the antigen, after the subject has been exposed to the antigen, or both.~~

~~24. Use of the compound according to any one of claims 1 to 18, for the preparation of a medicament for inducing tolerance to an antigen or for the treatment of an unwanted immune response.~~

~~25.~~36. A compound for the induction of antigen-specific immune tolerance in a subject, the compound comprising an antigen, a polymeric linker comprising a polymeric portion, and a liver targeting moiety;

wherein the linker is bonded to the antigen via a disulfide bond or a disulfanyl ethyl ester;

wherein the disulfide bond or the disulfanyl ethyl ester are each configured to be cleaved upon administration of the compound to the subject and to release the antigen from the polymeric linker;

wherein the polymeric linker comprises a terminal end unit lacking each of a dithioester and a dithiobenzoate (DTB) and wherein the terminal end unit confers improved stability to the compound when in solution.

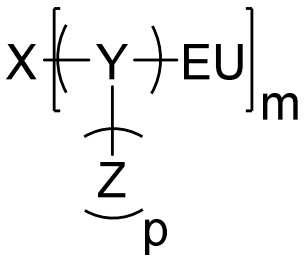
~~26.~~37. The compound of claim ~~25~~36, wherein the polymeric portion is copolymeric and comprises a first repeat unit and a second repeat unit.

~~27.~~38. The compound of claim ~~26~~37, wherein the liver targeting moiety is connected to the first unit directly or through a connecting group of the first unit, wherein the first unit comprises a first C-amido or first C-carboxy functionality and the connecting group is an aliphatic group, a polyether, or a polyamino group.

~~28. The compound of claim 27, wherein the first unit comprises a first C-amido or first C-carboxy functionality and the connecting group is an aliphatic group, a polyether, or a polyamino group.~~

~~29.~~39. The compound of any one of claims ~~26~~36 to ~~28~~38, wherein the first repeat unit is a first acrylyl unit and the second repeat unit is a second acrylyl unit.

~~30.~~40. A antigen-specific tolerogenic compound comprising Formula 1:



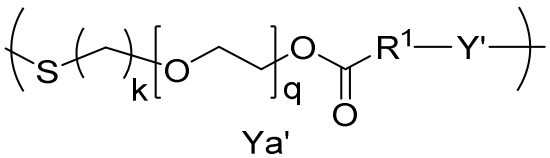
Formula 1

where:

m is an integer from about 1 to 100;

X comprises an antigen;

Y is of a linker moiety having a formula selected from the group consisting of:



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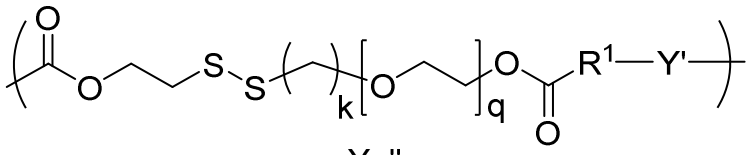

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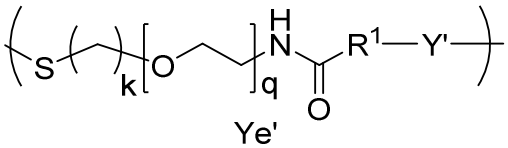

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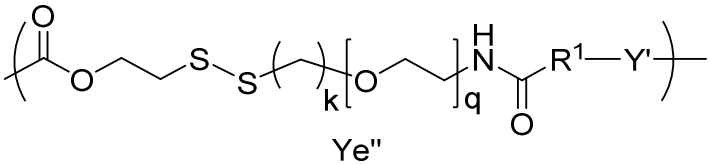

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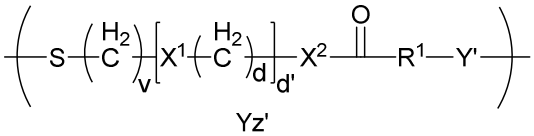

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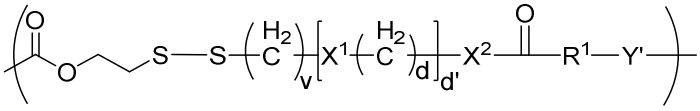


Yz''

wherein:

q is an integer from 0 to 100;

k is an integer from 0 to 10;

R_1 is selected from the group consisting of $-CH_2-$, $-(CH_2)_2-C(CH_3)(CN)-$, $-(CH_2)_2-C(CH_3)(CH_3)-$, $-(CH_2)_2-CH(CH_3)-$, and $-CH(CH_3)-$; and

X^1 and X^2 are independently selected from a direct bond, $-NR^6-$, and -O-;

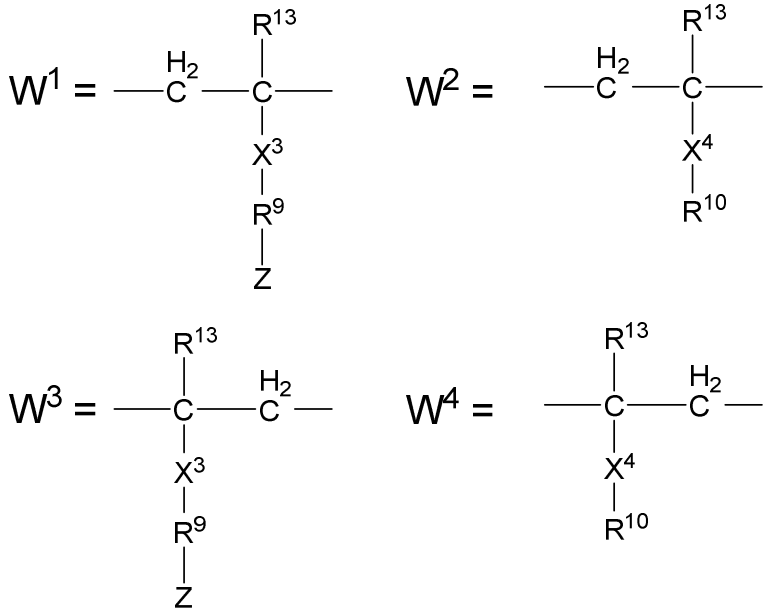
v is an integer from 0 to 10;

d is an integer from 0 to 5;

d' is an integer from 0 to 50;

R^6 is H or optionally substituted $C_{1\text{-}6}$ alkyl;

Y' is a random copolymer, gradient copolymer, or block copolymer of W^1 and W^2 or of W^3 and W^4, where W^1, W^2, W^3, and W^4 are as depicted below:



wherein the number of repeat units of W^1 or W^3 in Y is denoted as p and wherein p is an integer of at least about 1;

wherein the number of repeat units of W^2 or W^4 in Y is denoted as r and wherein r is an integer of at least about 1;

wherein the sum of p and r ranges from 100 to 200;

wherein

X^3 is selected from -C(O)-NH- or -C(O)O-;

X^4 is -C(O)-NH-, -C(O)O-, or -C(O)-OH;

R^9 is a direct bond or $-[((CH_2)_hX^5)_t-((CH_2)_{h'}X^6)_{t'}]-$;

where, X^5 and X^6 are independently selected from a direct bond, $-CNR^{6'}-$, and -O-;

where each instance of $R^{6'}$ is independently H or optionally substituted $-C_{1\text{-}6}$ alkyl;

R^{10} is not present, is H, or is $-[((CH_2)_{h''}X^7)_{t''}-((CH_2)_{h'''}X^8)_{t'''}]-H$;

where, X^7 and X^8 are independently selected from a direct bond, $-CNR^{6''}-$, and -O-;

where each instance of $R^{6''}$ is independently H or optionally substituted $-C_{1\text{-}6}$ alkyl;

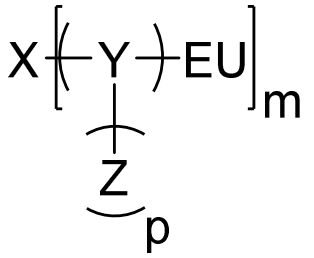
where t, t', h, h', t", t'", h", and h'" are each independently an integer of equal to or at least 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 20;

each instance of R^{13} is independently H, methyl, or optionally substituted -C_{1-6} alkyl;

EU is a terminal end unit, wherein EU comprises a carbon atom that is bonded to a carbon of the linker, thereby forming a carbon-carbon bond between the linker and the terminal end unit; and

Z comprises a liver-targeting moiety.

41. An antigen-specific tolerogenic compound comprising Formula 1:



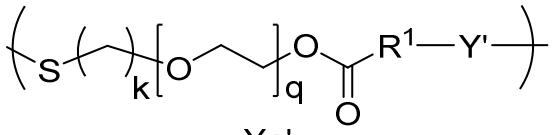
Formula 1

where:

m is an integer from 1 to 100;

X comprises a food antigen or a self antigen, wherein if presented to a subject apart from the compound, induces an unwanted immune response in the subject;

Y is of a linker moiety having a formula selected from the group consisting of:



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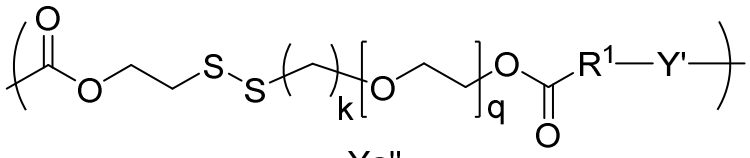

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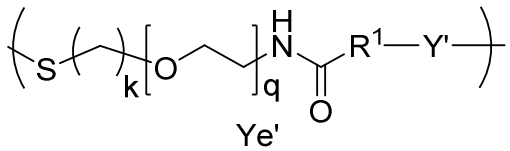

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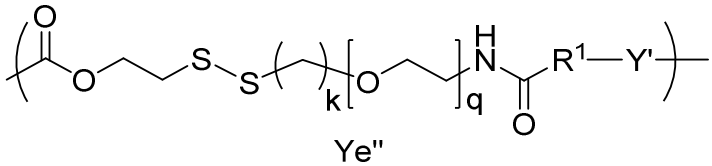

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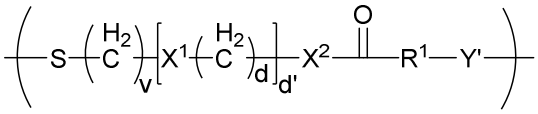

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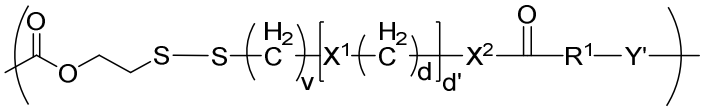


Yz''

wherein:

q is an integer from 0 to 100;

k is an integer from 0 to 10;

R_1 is selected from the group consisting of $-CH_2-$, $-(CH_2)_2-C(CH_3)(CN)-$, $-(CH_2)_2-C(CH_3)(CH_3)-$, $-(CH_2)_2-CH(CH_3)-$, and $-CH(CH_3)-$; and

X^1 and X^2 are independently selected from a direct bond, $-NR^6-$, and -O-;

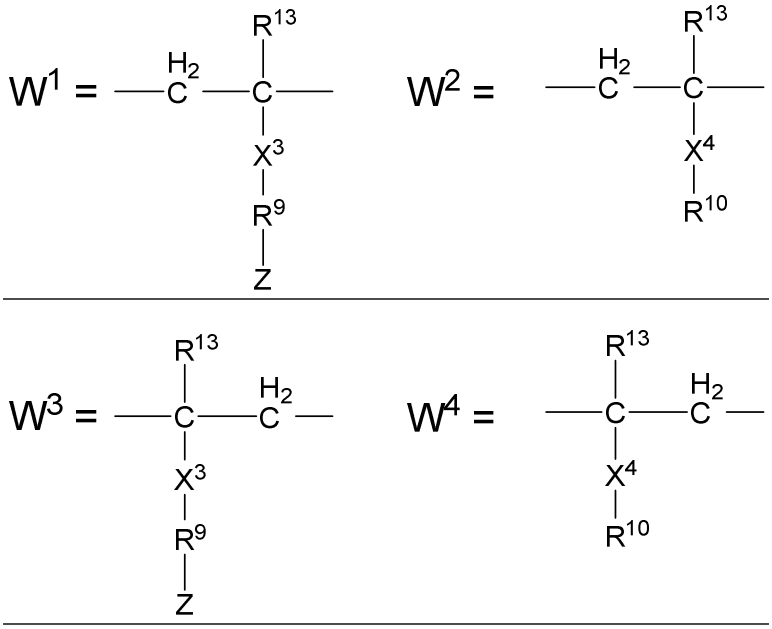
v is an integer from 0 to 10;

d is an integer from 0 to 5;

d' is an integer from 0 to 50;

R^6 is H or optionally substituted C_{1-6} alkyl;

Y' is a random copolymer, gradient copolymer, or block copolymer of W^1 and W^2 or of W^3 and W^4, where W^1, W^2, W^3, and W^4 are as depicted below:



wherein the number of repeat units of W^1 or W^3 in Y is denoted as p and wherein p is an integer of at least 1;

wherein the number of repeat units of W^2 or W^4 in Y is denoted as r and wherein r is an integer of at least 1;

wherein the sum of p and r ranges from 100 to 200;

wherein

X^3 is selected from -C(O)-NH- or -C(O)O-;

X^4 is -C(O)-NH-, -C(O)O-, or -C(O)-OH;

R^9 is a direct bond or $-[((CH_2)_hX^5)_t-((CH_2)_{h'}X^6)_{t'}]-$;

where, X^5 and X^6 are independently selected from a direct bond, $-CNR^{6'}-$, and -O-;

where each instance of $R^{6'}$ is independently H or optionally substituted $-C_{1-6}$ alkyl;

R^{10} is not present, is H, or is $-[((CH_2)_{h''}X^7)_{t''}-((CH_2)_{h'''}X^8)_{t'''}]-H$;

where, X^7 and X^8 are independently selected from a direct bond, $-CNR^{6''}-$, and -O-;

where each instance of $R^{6''}$ is independently H or optionally substituted $-C_{1-6}$ alkyl;

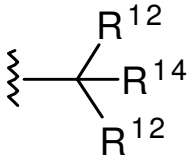
where t, t', h, h', t'', t''', h'', and h''' are each independently an integer of equal to or at least 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 20;

each instance of R^{13} is independently H, methyl, or optionally substituted -C_{1-6} alkyl;

EU is a terminal end unit, wherein EU comprises a carbon atom that is bonded to a carbon of the linker, thereby forming a carbon-carbon bond between the linker and the terminal end unit; and

Z comprises a glucosylating or galactosylating moiety.

~~31.~~42. The compound of claim ~~30~~40 or 41, wherein EU is represented by:



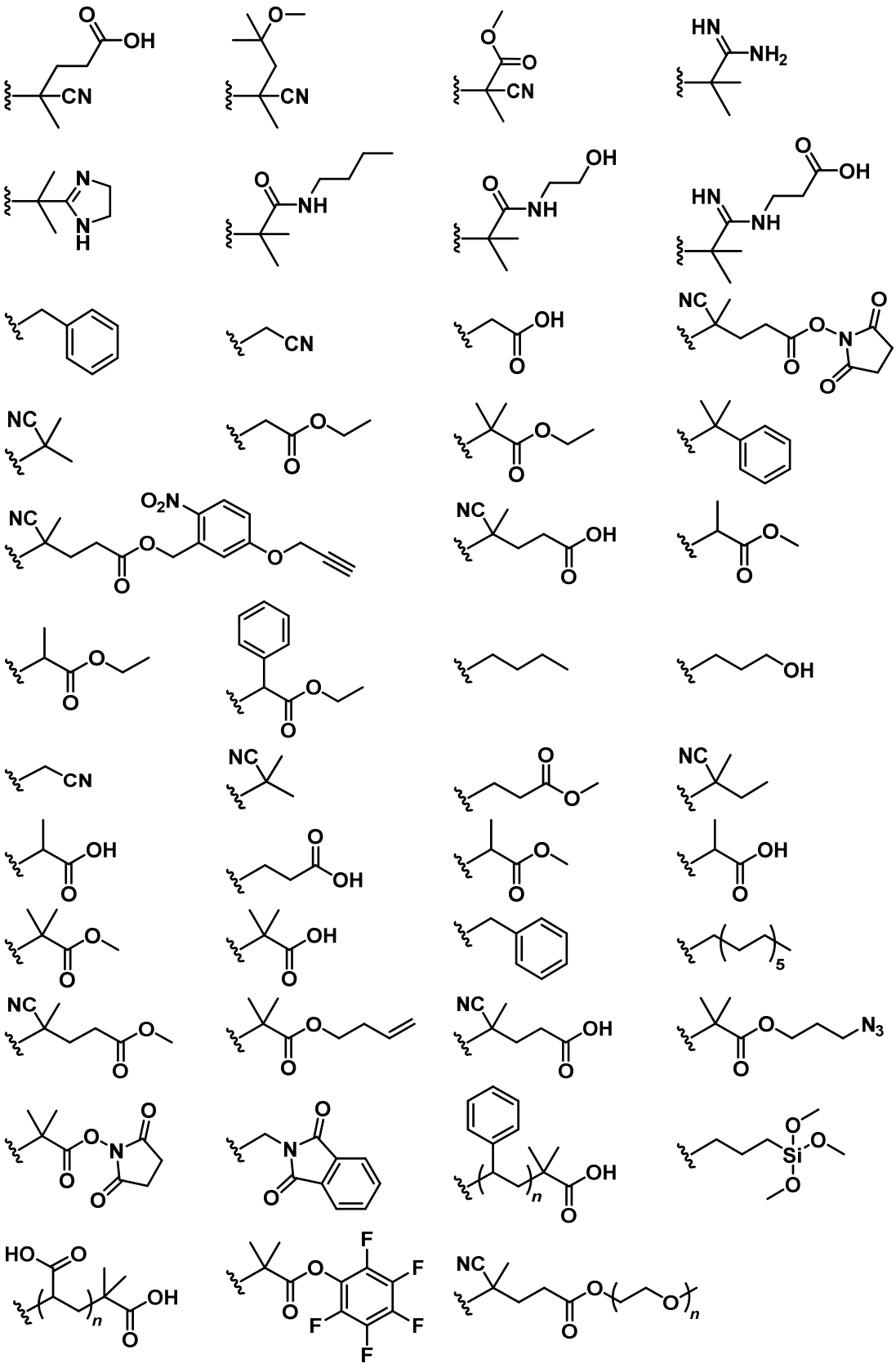
where R^{14} is selected from optionally substituted C_{1-11} alkyl; -CN; optionally substituted -C(=NH)NH_2; optionally substituted heterocyclyl; optionally substituted aryl; optionally substituted heteroaryl; optionally substituted aralkyl; optionally substituted heteroaralkyl; C-carboxy (-C(O)OR) where R is -H, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} alkylenyl, or optionally substituted phenyl; optionally substituted C-amido (-C(O)NR_AR_B) where R_A and R_B are independently -H or optionally substituted C_{1-6} alkyl; optionally substituted succinimidyl ester; optionally substituted isoindolin-1,3-dione; an alkyl silane; and

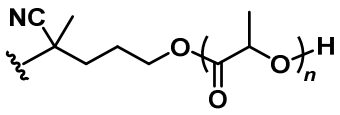
where each instance of R^{12} is independently a hydrogen, an C_{1-10} alkyl optionally substituted with halogen, C-carboxy, -amino, or -OH, or each instance of R^{12} is taken together to provide an optionally substituted C_{3-6} cycloalkyl.

~~32.~~43. The compound of claim ~~30~~ 42, wherein each optional substitution on an R^{14} is selected from C_{1-3} alkyl, C_{1-6} alkoxy, C_{1-6} alkylenyl, hydroxyl, amino, halogen, C-carboxy (where R is -H, C_{1-6} alkyl, or polyethylene glycol (PEG).

~~33.~~44. The compound of claim ~~1~~40 or 41, wherein EU is selected from the group consisting of:







~~34.~~45. The compound of ~~any one of~~ claim~~s 30 to 33~~ 40 or 41, wherein the ratio of p to r is ~~about~~ between 1:1 and 4:1.

~~35. The compound of any one of claims 30 to 33, wherein the ratio of p to r is about 4:1.~~

~~36.~~46. The compound of ~~any one of~~ claim~~s 30 to 33~~ 40 or 41, where Y is Ya' and:

k is 2;

R^1 is -$(CH_2)_2$-$C(CH_3)(CN)$-;

X^3 is -C(O)-NH-, h is 2, X^5 is -O-, t is 2, and t' is 0, such that X^3 and R^9 taken together is -C(O)-NH-CH_2-CH_2-O-CH_2-CH_2-O-.

~~37.~~47. The compound of ~~any one of~~ claim~~s 30 to 33~~ 40 or 41, where Y is Ye' and where:

q is 0;

k is 2;

R^1 is -$(CH_2)_2$-$C(CH_3)(CN)$-;

X^3 and R^9 taken together is -C(O)-NH-$(CH_2)_2$-$(O$-CH_2-$CH_2)_t$-;

t is 1; and

Z is one or more of galactose, glucose, galactosamine, glucosamine, N-acetylgalactosamine, or N-acetylglucosamine.

~~38.~~48. The compound of claim ~~36 or 37~~ 40 or 41, where q is between 0 and 3.

~~39. The compound of claim 36 or 37, where q is 3.~~

~~40.~~49. The compound of ~~any one of the preceding~~ claim~~s~~ 40 or 41, wherein, when in a solution of 10 mM sodium acetate and 274 mM sorbitol at a compound concentration of 1 mg/mL, at a temperature of 23 ºC to 27 ºC, the compound degrades less than 2.0% over a period of 28 days.

41.50. The compound of any one of the preceding claims 40 or 41, wherein the liver targeting moeity is galactose, glucose, galactosamine, glucosamine, N-acetylgalactosamine, and/or N-acetylglucosamine.

42.51. The compound of claim 4150, where Z is bound at its C1, C2 or C6 to Y.

43. The compound of claim 42, where Z is N-acetylgalactosamine or N-acetylglucosamine.

44.52. The compound of any one of the preceding claims 40 or 41, wherein the antigen is a tolerogenic portion of a full-length antigen.

45.53. The compound of any one of the preceding claims 52, where the antigen comprises a food antigen.

46.54. The compound of claim 45 53, wherein the food antigen is selected from the group consisting of conarachin (Ara h 1), allergen II (Ara h 2), arachis agglutinin, conglutin (Ara h 6), 31 kda major allergen/disease resistance protein homolog (Mal d 2), lipid transfer protein precursor (Mal d 3), major allergen Mal d 1.03D (Mal d 1), a-lactalbumin (ALA), lactotransferrin, actinidin (Act c 1, Act d 1), phytocystatin, thaumatin-like protein (Act d 2), kiwellin (Act d 5), ovomucoid, ovalbumin, ovotransferrin, and lysozyme, livetin, apovitillin, vosvetin, 2S albumin (Sin a 1), 1 lS globulin (Sin a 2), lipid transfer protein (Sin a 3), profilin (Sin a 4), profilin (Api g 4), high molecular weight glycoprotein (Api g 5), Pen a 1 allergen (Pen a 1), allergen Pen m 2 (Pen m 2), tropomyosin fast isoform, high molecular weight glutenin, low molecular weight glutenin, alpha-, gamma- and omega-gliadin, hordein, secalin, avenin, major strawberry allergy Fra a 1-E (Fra a 1), and profilin (Mus xp 1), a portion of any of said antigens, and a mimetic of any of said antigens.

47.55. The compound of claim 53, wherein the food antigen is selected from the group consisting of high molecular weight glutenin, low molecular weight glutenin, alpha-, gamma- and omega-gliadin, hordein, secalin, and avenin, a portion of any of said antigens, and a mimetic of any of said antigens.

48.56. The compound of claim 4553, wherein the food antigen is associated with celiac disease.

49.57. The compound of any one of the preceding claims 52, wherein the antigen is a self antigen and where the antigen is associated with an autoimmune disease.

50.58. The compound of Claim 57, wherein the autoimmune disease is selected from the group consisting of Type I diabetes, multiple sclerosis, rheumatoid arthritis, vitiligo, uveitis, pemphis vulgaris, neuromyelitis optica, Goodpasture's Disease, Parkinson's disease, myasthenia gravis, celiac disease, and anti-neutrophil cytoplasmic antibody-associated vasculitis.

51. The compound of any one of the preceding claims, where the antigen comprises a self antigen.

52.59. The compound of claim 5157, wherein the self antigen is selected from myelin basic protein, myelin oligodendrocyte glycoprotein, myelin basic protein, and proteolipid protein, a portion of any of said antigens, and a mimetic of any of said antigens.

53.60. The compound of claim 51 57, wherein the self antigen is selected from insulin, proinsulin, preproinsulin, glutamic acid decarboxylase-65 (GAD-65), GAD-67, insulinomaassociated protein 2 (IA-2), and insulinoma-associated protein 213 (IA-213), ICA69, ICA12 (SOX-13), carboxypeptidase H, Imogen 38, GLIMA 38, chromogranin- A, HSP-60, caboxypeptidase E, peripherin, glucose transporter 2, hepatocarcinoma-intestinepancreas/pancreatic associated protein, S100β, glial fibrillary acidic protein, regenerating gene II, pancreatic duodenal homeobox 1, dystrophia myotonica kinase, islet-specific glucose-6- phosphatase catalytic subunit-related protein, SST G-protein coupled receptors 1-5, myeloperoxidase (MPO), and proteinase-3/myeloblastin (PR3), and a portion of any of said antigens, and a mimetic of any of said antigens.

54. The compound of any one of the preceding claims, where the antigen comprises a therapeutic agent.

55. The compound of claim 54, wherein the therapeutic agent is selected from Abciximab, Adalimumab, Agalsidase alfa, Agalsidase beta, Aldeslukin, Alglucosidase alfa, Factor VIII, Factor IX, Infliximab, L asparaginase, Laronidase, Natalizumab, Octreotide, Phenylalanine ammonia lyase (PAL), Rasburicase (uricase), a gene therapy vector, or AAV, a portion of any of said antigens, and a mimetic of any of said antigens.

~~56. The compound of any one of the preceding claims, where the antigen comprises a transplant antigen.~~

~~57. The compound of claim 56, wherein the transplant antigen is selected from the group consisting of subunits of the MHC class I and MHC class II haplotype proteins and their complexes with the antigens they present, and minor blood group antigens RhCE, Kell, Kidd, Duffy and Ss.~~

~~58.~~61. The compound of ~~any one of the preceding~~ claim~~s~~ 57, where<u>in</u> the <u>self</u> antigen ~~or a tolerogenic portion thereof is~~ <u>is associated with pemphigus vulgaris and wherein the self antigen comprises one or more of</u> desmoglein-3, <u>desmoglein</u>-1, ~~and/~~or <u>desmoglein</u>-4.

~~59. The compound of any one of the preceding claims, where the antigen or a tolerogenic portion thereof is associated with pemphigus vulgaris.~~

~~60.~~62. A composition comprising the compound of ~~any one of the preceding~~ claim~~s~~ <u>40 or 41</u>.

~~61.~~63. The ~~U~~<u>u</u>se of a compound according to ~~any one of the preceding~~ claim~~s~~ <u>40 or 41~~,~~ in the manufacture of a medicament</u> for ~~use in inducing tolerance to the antigen~~<u>the treatment of an unwanted immune response</u>.

~~62. A method of inducing tolerance to an antigen to which a subject is capable of developing an unwanted immune response, comprising administering a compound any one of the preceding claims to the subject.~~

~~63. The method of claim 62, wherein the compound is administered prior to the subject being exposed to the antigen, after the subject has been exposed to the antigen, or both.~~

~~64. Use of the compound according to any one of the preceding claims for the preparation of a medicament for inducing tolerance to an antigen.~~

65. The compound of any one of the preceding claims, wherein the antigen comprises a foreign transplant antigen, a tolerogenic portion thereof, or a mimetic thereof against which transplant recipients develop an unwanted immune response.

66. The compound or composition of any one of the preceding claims, wherein the antigen comprises a foreign food, animal, plant or environmental antigen, a tolerogenic portion of any of thereof, or a mimetic of any of thereof against which induces patients develop an unwanted immune response.

67. The compound or composition of any one of the preceding claims, wherein the antigen comprises a foreign therapeutic agent, a tolerogenic portion thereof, or a mimetic thereof against which patients develop an unwanted immune response.

68. The compound or composition of any one of the preceding claims, wherein the antigen comprises a self antigen, a tolerogenic portion thereof, or a mimetic thereof against the endogenous version of which patients develop an unwanted immune response or a tolerogenic portion thereof.

69. The compound or composition of any one of the preceding claims, wherein the antigen comprises an antibody, antibody fragment or ligand that specifically binds a circulating protein or peptide or antibody, which circulating protein or peptide or antibody is causatively involved in transplant rejection, immune response against a therapeutic agent, autoimmune disease, hypersensitivity and/or allergy.

70. A pharmaceutically acceptable composition for inducing tolerance to a therapeutic protein in a subject having a deficiency in production of a functional analogous native protein, comprising the compound of any one of the preceding claims.

71. Use of the compound or composition of any one of the prededing claims for treating an unwanted immune response against an antigen.

72. The use of claim 71, wherein the unwanted immune response is associated with Type I diabetes, multiple sclerosis, rheumatoid arthritis, vitiligo, uveitis, pemphigus vulgaris,

~~neuromyelitis optica, Parkinson's disease, Goodpasture's disease, celiac disease, or myasthenia gravis.~~

~~73. The compound or composition of any one of the preceding claims for manufacturing a medicament for use in treating an unwanted immune response against an antigen.~~

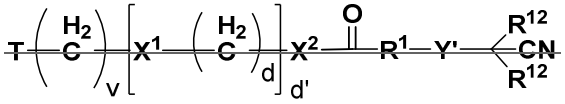
~~74.~~64. A method of manufacturing an antigen-specific tolerogenic compound, comprising:

preparing a polymeric portion of a polymeric linker using reversible addition-fragmentation chain transfer reaction (RAFT);

displacing a chain transfer agent remnant from the polymeric portion with a terminal end unit; and

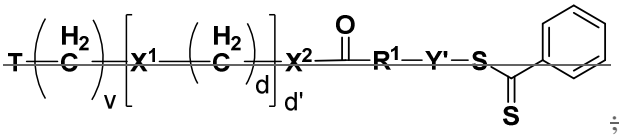
conjugating an antigen to the polymeric linker.

~~75. A method of manufacturing a compound having the following structure:~~



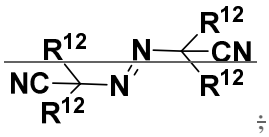
~~comprising:~~

~~providing a dithiobenzoate containing compound of the following structure:~~



~~;~~

~~providing a terminal end unit of the following structure:~~



~~;~~

~~mixing the terminal end unit reagent with the dithiobenzoate containing compound to form the compound;~~

~~wherein T, when present, is PDS or a carboxylic acid;~~

~~X^1 and X^2 are independently selected from a direct bond, NR^6, and O ;~~

~~R^6 is H or C_{1-6} alkyl optionally substituted with a halogen, C_{1-3} alkyl or C carboxy;~~

~~v is an integer from 0 to 10;~~

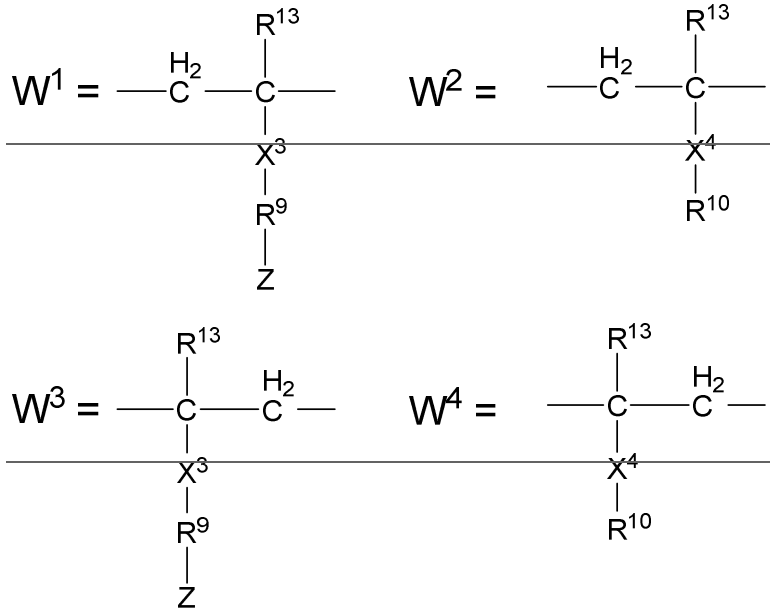
~~d is an integer from 0 to 5;~~

~~d' is an integer from 0 to 50;~~

~~wherein each instance of R^{12} is independently hydrogen or an optionally substituted alkyl;~~

~~wherein R_1 is selected from the group consisting of $-CH_2-$, $-(CH_2)_2-C(CH_3)(CN)-$, $-(CH_2)_2-C(CH_3)(CH_3)-$, $-(CH_2)_2-CH(CH_3)-$, and $-CH(CH_3)-$~~

~~wherein Y' is a random copolymer, gradient copolymer, or block copolymer of W^1 and W^2 or of W^3 and W^4, where W^1, W^2, W^3, and W^4 are as depicted below:~~



~~wherein the number of repeat units of W^1 or W^3 in Y' is denoted as p and wherein p is an integer of at least about 1;~~

~~wherein the number of repeat units of W^2 or W^4 in Y' is denoted as r and wherein r is an integer of at least about 1;~~

~~wherein~~

~~X^3 is selected from $-C(O)-NH-$ or $-C(O)O-$;~~

~~X^4 is $-C(O)-NH-$, $-C(O)O-$, or $-C(O)-OH$;~~

~~R^9 is a direct bond or $-[((CH_2)_hX^5)_t-((CH_2)_hX^6)_t]-$;~~

where, X^5 and X^6 are independently selected from a direct bond, $-CNR^{6'}-$, and $-O-$;

where each instance of $R^{6'}$ is independently H or C_{1-6} alkyl optionally substituted with halogen, C_{1-3} alkyl or C-carboxy;

R^{10} is not present or is $-[((CH_2)_{h'-z}X^7)_{t'-}((CH_2)_{h''-z}X^8)_{t''}]-H$;

where, X^7 and X^8 are independently selected from a direct bond, $-CNR^{6''}-$, and $-O-$;

where each instance of $R^{6''}$ is independently H or $-C_{1-6}$ alkyl optionally substituted with halogen, C_{1-3} alkyl or C-carboxy;

where t, t', h, and h' are each independently an integer of equal to or at least about: 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20;

where t'', t''', h'', and h''' are each independently an integer of equal to or at least about: 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20;

each instance of R^{13} is independently H, methyl, or optionally substituted C_{1-6} alkyl; and

Z comprises a liver-targeting moiety.

76.65. A method of manufacturing an antigen-specific tolerogenic compound, comprising:

coupling a liver targeting moiety to a first acrylyl monomer;

preparing a polymeric portion of a polymeric linker using reversible addition-fragmentation chain transfer reaction (RAFT) of at least the first acrylyl monomer and a second acrylyl monomer, the polymeric portion comprising a copolymer comprising a first acrylyl unit and a second acrylyl unit, the first acrylyl unit comprising a first C-amido or C-carboxy functionality and the second acrylyl unit comprising a second C-amido or C-carboxy functionality;

displacing a chain transfer agent remnant from the polymeric portion with a terminal end unit wherein the terminal end unit confers improved stability to the compound when in solution; and

conjugating an antigen to the polymeric linker, wherein the antigen to which tolerance is desired, when presented alone to the subject is capable of inducing an unwanted immune response in the subject.

~~77.~~66. The method of claim ~~76~~65, wherein the terminal end unit is added to the polymeric portion by reaction using a bis-azo compound.

~~78.~~67. The method of claim ~~76 or 77~~65, wherein the second acrylyl monomer is coupled to an aliphatic group, an alcohol, or an aliphatic alcohol~~.~~.

68. The method of Claim 65, wherein the terminal end unit is provided by performing a reaction between an azo compound and a precursor to the polymeric linker, the precursor comprising a dithioester, a dithiobenzoate, a trithiocarbonate, or a xanthate.

69. The method of Claim 65, wherein the azo compound is azobisisobutyronitrile (AIBN).

70. The method of Claim 65, wherein terminal end unit is isobutyronitrile.

~~79.~~71. A compound for the induction of antigen-specific immune tolerance in a subject, the compound comprising an antigen, a polymeric linker comprising a polymeric portion, and a liver targeting moiety;

wherein the linker is bonded to the antigen via a disulfide bond or a disulfanyl ethyl ester;

wherein the disulfide bond or the disulfanyl ethyl ester are each configured to be cleaved upon administration of the compound to the subject and to release the antigen from the polymeric linker;

wherein the polymeric linker comprises a terminal end unit that confers improved stability to the compound when in solution; and

wherein the terminal end unit is not –H, a dithioester, a dithiobenzoate, a trithiocarbonate, or a xanthate.

~~80. The compound of any one of Claims 1 to 48, wherein the antigen comprises all or an immunogenic fragment of SEQ ID NO: 54, 55, 56, 57, 60, or 61.~~

~~81. The compound of any one of Claims 1 to 44 or 49 to 52, wherein the antigen comprises all or an immunogenic fragment of SEQ ID NO: 21, 27, 28, 30, 32, 43, 44, or 46.~~

~~82. The compound of any one of Claims 1 to 44, 49 to 51 or 53, wherein the antigen comprises all or an immunogenic fragment of SEQ ID NO: 1 to SEQ ID NO: 19.~~